CLINICAL INVESTIGATIONS

A Risk Score to Predict Arrhythmias in Patients with Unexplained Syncope

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Abstract

Objectives: To develop and validate a risk score predicting arrhythmias for patients with syncope remaining unexplained after emergency department (ED) noninvasive evaluation. **Methods:** One cohort of 175 patients with unexplained syncope (Geneva, Switzerland) was used to develop and cross-validate the risk score; a second cohort of 269 similar patients (Pittsburgh, PA) was used to validate the system. Arrhythmias as a cause of syncope were diagnosed by cardiac monitoring or electrophysiologic testing. Data from the patient's history and 12-lead emergency electrocardiography (ECG) were used to identify predictors of arrhythmias. Logistic regression was used to identify predictors for the risk-score system. Risk-score performance was measured by comparing the proportions of patients with arrhythmias at various levels of the score and receiver operating characteristic (ROC) curves. **Results:** The prevalence of arrhythmic syncope was 17% in the derivation cohort and 18% in the validation cohort. Predictors of arrhythmias were abnormal ECG (odds ratio [OR]: 8.1, 95% confidence interval [CI] = 3.0 to 22.7), a history of congestive heart failure (OR: 5.3, 95% CI = 1.9 to 15.0), and age older than 65 (OR: 5.4, 95% CI = 1.1 to 26.0). In the derivation cohort, the risk of arrhythmias ranged from 0% (95% CI = 0 to 6) in patients with no risk factors to 6% (95% CI = 1 to 15) for patients with one risk factor, 41% (95% CI = 26 to 57) for patients with two risk factors, and 60% (95% CI = 32 to 84) for those with three risk factors. In the validation cohort, these proportions varied from 2% (95% CI = 0 to 7) with no risk factors to 17% (95% CI = 10 to 27) with one risk factor, 35% (95% CI = 24 to 46) with two risk factors, and 27% (95% CI = 6 to 61) with three risk factors. Areas under the ROC curves ranged from 0.88 (95% CI = 0.84 to 0.91) for the derivation cohort to 0.84 (95% CI = 0.77 to 0.91) after cross-validation within the same cohort and 0.75 (95% CI = 0.68 to 0.81) for the external validation cohort. **Conclusions:** In patients with unexplained syncope, a risk score based on clinical and ECG factors available in the ED identifies patients at risk for arrhythmias. **Key words:** unexplained syncope; arrhythmia; risk factor; scoring system. ACADEMIC EMERGENCY MEDICINE 2003; 10:1312–1317.

Syncope is a common clinical problem in the emergency department (ED) that can be disabling to the patient, difficult to diagnose for the physician, and that frequently leads to extensive cardiovascular testing.[1] Current recommendations for the evaluation of this symptom begin with a thorough clinical history, physical examination, and 12-lead electrocardiography (ECG). These noninvasive tests lead to a diagnosis for syncope in approximately 50% of cases.[2–5] Among patients with syncope remaining unexplained after this initial evaluation, one critical issue for ED physicians is the identification of those at

low and high risk for significant arrhythmias as the cause of syncope, many of them now being treatable with drugs and/or devices.[6,7] Concerns that these sometimes well-appearing patients are at risk for arrhythmias and subsequent sudden death has fueled extensive, and sometimes unnecessary, broad-based cardiovascular evaluations and frequent hospital admissions.[8,9]

In clinical practice, assessment of a patient's individual risk of significant arrhythmias is a difficult challenge. Therefore, identification of patients who are at low risk for arrhythmias would help ED physicians to make informed decisions about patients' in-hospital admission and/or the need for specialized cardiovascular testing.[10] The goals of this study were to develop and validate, using clinical and ECG features available in the ED, a risk score predicting arrhythmias in patients with syncope that remained unexplained by clinical history, physical examination, and 12-lead ECG.

METHODS

Study Design. This was a derivation-validation study aimed at developing a clinical prediction rule for arrythmias in patients with unexplained syncope.

Both studies were approved by their institutional review board. Written informed consent was obtained from each patient before his or her enrollment.

Study Setting and Population. The derivation cohort included patients recruited between 1998 and 2000 at the Hôpital Cantonal, the main teaching hospital of the University of Geneva Medical School (Geneva, Switzerland).[11] Patients in the validation cohort were recruited between 1989 and 1991 at the University of Pittsburgh Medical Center (Pittsburgh, PA). Both institutions are the major primary and tertiary care hospitals for their area.

In both centers, all patients 18 years of age or older who came to the ED during the study period with a chief complaint of syncope were prospectively included. Patients were identified from daily visits by one of the investigators. Syncope was defined as sudden transient loss of consciousness with an inability to maintain postural tone, and with spontaneous recovery. Patients with symptoms clearly compatible with seizure disorder, vertigo, dizziness, coma, shock, or other states of altered consciousness were not included.

Study Protocol. In both centers, patients included underwent in the ED an identical, standardized, noninvasive evaluation including: a complete clinical history, physical, and neurologic examination; a laboratory evaluation (hematocrit, serum levels of creatine kinase and glucose); 12-lead ECG; and testing for orthostatic hypotension. This standardized evaluation was performed and interpreted by a full-time research physician under the supervision of one of the investigators.

After the initial evaluation, patients were classified into two groups: (1) those in whom a cause of syncope was strongly suspected based on history and physical examination (i.e., vasovagal and situational syncope), blood pressure measurements (i.e., orthostatic hypotension), or 12-lead ECG (e.g., third-degree atrioventricular block); and (2) those in whom the cause of syncope was not diagnosed by the history, physical examination, or 12-lead ECG. This latter group of patients, further referred as unexplained syncope, were included in the study because arrhythmias often are a concern.

Evaluation of Patients with Unexplained Syncope. In the derivation cohort, patients with unexplained syncope underwent: (1) a targeted diagnostic procedure(s), when a specific disorder requiring confirmation by selected test(s) was suspected by suggesting signs or symptoms (e.g., echocardiography for suspected aortic stenosis); and/or (2) sequential cardiovascular testing when no specific clinical entity was suspected or the targeted test was negative. Cardiovascular tests included in all patients: transthoracic

echocardiography; 24-hour Holter monitoring; continuous-loop event recorder; and passive upright tilt testing. Based on current recommendations, electrophysiologic studies were restricted to patients with structural heart disease and/or an abnormal ECG.[12] In the validation cohort, cardiovascular work-up was similar with respect to arrhythmias outcome: all patients with unexplained syncope were hospitalized and had prolonged ECG monitoring of at least 24-hour duration. Electrophysiologic studies were performed in patients with heart disease and/or an abnormal ECG, based on the recommendations of a consulting cardiologist. Targeted diagnostic procedure(s) were performed when a specific disorder was suspected by suggesting signs or symptoms (e.g., echocardiography for suspected aortic stenosis). On the other hand, upright tilt testing and continuous-loop recording were not performed systematically because they were not available in the late 1980s.

Measures. Key domains of data collection were: (1) patient's demographic and clinical data; (2) clinical features pertaining to physical examination at the time of admission; and (3) results of basic laboratory, 12-lead ECG, and specialized cardiovascular testing. Information on the number of syncopal episodes, precipitating factors, and the occurrence of prodromal and recovery symptoms (such as palpitations, diaphoresis, blurred vision) also were collected in a standardized fashion. Specific symptoms suggesting specific clinical entities such as seizures, pulmonary embolism, or aortic stenosis also were collected.

The 12-lead baseline ECG was classified as abnormal, but nondiagnostic, in the presence of the following abnormalities: (1) atrial fibrillation; (2) sinus pause ≥ 2 and <3 seconds; (3) sinus bradycardia with heart rate of >35 beats per minute and ≤ 45 beats per minute; (4) conduction disorders (e.g., bundle branch block, second-degree Mobitz I atrioventricular block, bifascicular block); (5) signs of old myocardial infarction or ventricular hypertrophy; and (6) multiple premature ventricular beats. An ECG was classified as normal even in the presence of first-degree atrioventricular block, nonspecific ST-T segment abnormalities, sinus tachycardia, and premature atrial contractions.

Diagnostic Criteria for Cardiac Arrhythmias in Patients with Unexplained Syncope. Presumed diagnoses by the house staff or attending physicians were not accepted. Specialized diagnostic tests were performed and interpreted by cardiologists in accordance with published diagnostic criteria.[6,7,12] These diagnostic criteria were similar in both cohorts (derivation and validation).

Electrocardiographic monitoring (24-hour Holter or loop recorder) was considered to be diagnostic of syncope in the presence of syncope or near-syncope

and simultaneous occurrence of the following arrhythmias: (1) sinus pause ≥3 seconds; (2) sinus bradycardia ≤35 beats per minute; (3) atrial fibrillation with slow ventricular response (respiratory rate interval ≥3 seconds); (4) second-degree (Mobitz II) atrioventricular block; (5) complete atrioventricular block; and (6) symptomatic or sustained (≥30 seconds) ventricular tachycardia.

Results of electrophysiologic studies considered as diagnostic included: (1) prolonged corrected sinus node recovery time (≥550 msec) as indicative of sinus node disease; (2) prolonged H-V interval (≥100 msec); (3) supraventricular tachycardia 180 beats per minute or associated with hypotension; (4) sustained ventricular tachycardia; and (5) spontaneous infra-Hisian block.

Data Analysis. Variables in the two cohorts (derivation and validation sets) were compared using Student's t-test for continuous variables and the chi-square or Fisher exact test for dichotomous variables.

The primary goal of the analysis was to identify, among patients with unexplained syncope, which clinical factors were significantly associated with cardiac arrythmias. Descriptive statistics were applied for all variables collected. The univariate relation between baseline characteristics and presence of diagnostic arrhythmias was examined by the chi-square test for categorical variables and Student's t-test for continuous variables. Potential predictor variables included demographic information (age, gender), comorbid conditions (e.g., history of congestive heart failure, known coronary heart disease), history of prior syncope, the presence of symptoms before the syncopal episode, and ECG status. Univariate predictor variables associated with arrhythmias considered to be diagnostic of syncope were incorporated into a multivariate logistic regression model. For all analyses, a 2-tailed $p < 0.05$ indicated statistical significance.

A simple diagnostic score was computed from the logistic regression model, assigning numerical values to each independent predictor variable. First, we assigned one point to all predictors, weighting them equally. Second, we tested the consequences of assigning individual values to each predictor in proportion to their regression coefficients. The usefulness of this risk score predicting arrhythmias was measured by calculating the proportion of patients with diagnostic arrhythmias at various level of the score value in the derivation and the validation cohort.

Because the number of events (diagnostic arrhythmias) was small relative to the number of possible predictors considered, we were concerned that the selected model may have been overfitted. To examine the degree of overfitting of the prediction model to the development sample, we performed both a cross-validation and an external validation procedure. Cross-validation only eliminates overadjustment of

the prediction model to a specific sample drawn from a given population, whereas external validation eliminates both overfitting due to sample idiosyncrasies and overfitting due to true differences between patient populations. To conduct the cross-validation procedure,[13] the sample was split at random into 10 equal groups. A logistic regression model predicting diagnosis of arrhythmias was developed on nine tenths of the sample, and the resulting equation was applied to the remaining tenth; this procedure was repeated 10 times, each time rotating the cross-validation subset. A cross-validated score was built by extracting for each patient the cross-validated probability of arrhythmias. Because each prediction equation could take any of 4 values (corresponding to the presence of 0, 1, 2, or 3 predictors), and 10 equations were used to derive the cross-validated scores, these scores could take any of 40 values. The ability of the cross-validated scores to discriminate between patients with and without arrhythmias was examined by comparing the area under the receiver operating characteristic (ROC) curve with that obtained from the naive prediction scores, without cross-validation. External validation consisted in comparing the performance of the risk score in the derivation (Geneva) and the validation (Pittsburgh) sets using areas under the ROC curves. These areas were determined by the method of maximum likelihood ratio estimation. Confidence intervals of 95% were used, based on exact method (StatXact, Cytel Software, Cambridge, MA). Statistical testing was performed using SPSS version 9.0 (SPSS Inc., Chicago, IL).

RESULTS

In Geneva (derivation set), 617 patients were seen in the ED with syncope during the study period. Noninvasive assessment found the cause of syncope in 442 of them. The analysis for the predictors of arrhythmias were performed in the 175 remaining patients corresponding to the definition of unexplained syncope. In Pittsburgh (validation set), 668 patients with syncope were evaluated, and 267 of them were considered as having unexplained syncope. The demographic and clinical characteristics of patients with unexplained syncope are shown in Table 1. Patients in the derivation cohort were significantly older and had more past episodes of syncope. Except for myocardial infarction and essential hypertension, the proportion of patients with comorbid conditions was similar in the two populations. Table 2 depicts the spectrum of cardiac and noncardiac diseases causing syncope in the study populations. The proportion of patients in whom arrhythmia was considered to be diagnostic of syncope was similar in the derivation (17%) and in the validation (18%) cohort.

In the derivation cohort, significant univariate predictors of arrhythmias included an abnormal

TABLE 1. Demographic and Clinical Characteristics of Derivation and Validation Cohorts

	Derivation Cohort (n = 175)	Validation Cohort (n = 267)	p
Age (y)			
Mean (±SD)	65.6 (±17)	56.1 (±21)	<0.001
Range	19–90	17–94	
No. ≥65 years (%)	83 (47)	110 (41)	0.2
No. ≥75 years (%)	73 (42)	61 (23)	<0.001
Male gender (%)	94 (54)	109 (41)	0.008
Previous syncopal episode (%)			
First	98 (56)	86 (34)	<0.001
One	42 (24)	55 (22)	0.4
Two or more	35 (20)	111 (44)	<0.001
Sudden syncope (%)	63 (36)	89 (34)	0.6
Comorbid conditions (%)			
Coronary artery disease	48 (27)	78 (29)	0.7
Previous myocardial infarction	25 (14)	21 (8)	0.02
Congestive heart failure	28 (16)	33 (12)	0.3
Hypertension	77 (44)	83 (31)	0.006
Diabetes mellitus	23 (13)	33 (12)	0.8
ECG results (%)			
Normal	58 (33)	104 (40)	0.2
ST/T waves abnormalities only	30 (17)	25 (10)	0.02
Abnormal	87 (50)	133 (50)	1
Conduction disorder*	35 (20)	80 (30)	0.02
Old myocardial infarction	21 (12)	26 (10)	0.5
Rhythm abnormalities†	25 (14)	48 (17)	0.3

*Bundle branch block, Mobitz I atrioventricular block, bifascicular block.
†Atrial fibrillation, sinus pause ≥2 and <3 seconds, sinus bradycardia >35 per minute and ≤45 per minute, multiple premature ventricular beats.

ECG, age older than 65 years, a history of congestive heart failure, a history of myocardial infarction, and a history of cardiac disease (any type). Multivariate predictors of arrhythmias were an abnormal ECG (odds ratio [OR] = 8.1, 95% confidence interval [CI] = 3.0 to 22.7), a history of congestive heart failure (OR = 5.3, 95% CI = 1.9 to 15.0), and age older than 65 (OR = 5.4, 95% CI = 1.1 to 26.0). These results are depicted in Table 3.

TABLE 2. Diagnosis of Syncope in the Derivation and Validation Cohorts

	Derivation Cohort (n = 175)	Validation Cohort (n = 267)	p
Cardiac (%)			
Arrhythmias	30 (17)	47 (18)	0.9
Ventricular tachycardia	18 (10)	19 (7)	0.2
Sinus pause or AV block	12 (7)	28 (10)	0.3
Organic heart disease*	16 (9)	18 (7)	0.4
Noncardiac (%)			
Vasovagal	11 (6)	14 (5)	0.7
Seizures/psychiatric	22 (13)	23 (9)	0.2
Others†	9 (5)	11 (4)	0.6
Unknown (%)			
Syncope of unknown origin	87 (50)	154 (58)	0.1

*Includes in the derivation cohort: severe aortic stenosis (n = 8) and pulmonary embolism (n = 8); includes in the validation cohort: aortic stenosis (n = 5), pulmonary embolism (n = 8), aortic dissection (n = 1), and myocardial infarction (n = 4).
†Includes stroke, transient ischemic attack, mastocytosis (one case), and subarachnoid hemorrhage (one case).

We used the number of predictors present (0, 1, 2, 3) and assigned one point to each of them to define risk strata among patients. Table 4 depicts the distribution of patients across those risk strata. In the derivation cohort, the risk of arrhythmias ranged from 0% (95% CI = 0 to 6) in patients with no risk factors to 6% (95% CI = 1 to 15) for patients with one risk factor, 41% (95% CI = 26 to 57) for patients with two risk factors, and 60% (95% CI = 32 to 84) for those with three risk factors (Figure 1). In the validation cohort, the proportions of patients with arrhythmias in each risk group varied from 2% (95% CI = 0 to 7) for patients with no risk factors to 17% (95% CI = 10 to 27) for patients with one risk factor, 35% (95% CI = 24 to 46) for patients with two risk factors, and 27% (95% CI = 6 to 61) for patients with three risk factors.

The areas under the ROC curves ranged from 0.88 (95% CI = 0.84 to 0.91) for the derivation cohort, to 0.84 (95% CI = 0.77 to 0.91) after cross-validation, and 0.75 (95% CI = 0.68 to 0.81) after external validation.

We also tested one different scoring system, according to the individual regression coefficient

TABLE 3. Predictors of Cardiac Arrhythmias in Patients with Unexplained Syncope

	Univariate Analysis			Multivariate Analysis		
Variables	OR	95% CI	p	OR	95% CI	p
Abnormal ECG	11.6	4.6–29.5	<0.001	8.1	3.0–22.7	<0.001
Age ≥65 years	13.4	3.0–58.5	<0.001	5.4	1.1–26.0	0.03
History of congestive heart failure	8.6	3.5–21.1	<0.001	5.3	1.9–15.0	0.002
History of myocardial infarction	4.3	1.7–10.9	0.003			
History of cardiac disease (any type)	4.3	1.8–10.1	0.001			

TABLE 4. Distribution of Patients across Risk Strata

Number of Risk Factors	Number (%) from Derivation Cohort ($n = 175$)	Number (%) from Validation Cohort ($n = 267$)
0	62 (35)	94 (35)
1	54 (31)	81 (30)
2	44 (25)	81 (30)
3	15 (9)	11 (4)

values. The performance of this latter score, however, was not statistically different from the baseline analysis.

DISCUSSION

In this study, we identified the main clinical characteristics associated with cardiac arrhythmias in a cohort of patients with syncope that remained unexplained after ED noninvasive clinical evaluation (i.e., clinical history, physical examination, and 12-lead ECG), and combined them into an easily computed score predicting the risk of arrhythmias. This score, based on noninvasive clinical data (age ≥65, history of congestive heart failure, and abnormal ECG status), allowed us to classify patients into four risk categories with a fair degree of accuracy.

Syncope is difficult to evaluate in the ED. If a cause can be determined on the basis of initial clinical assessment, management decisions are relatively straightforward. However, in up to 50% of patients, a cause is not apparent on initial history, physical examination, and ECG. Under these circumstances, the fear for arrhythmias that may be inapparent in initial clinical assessment frequently leads to excessive cardiac testing and subsequent hospital admissions. Our model estimated the risk of severe arrhythmias to be very low (i.e., 2%, with 95% CI

Figure 1. Proportion of observed arrhythmias in the derivation and validation cohorts as a function of the number of risk factors.

ranging from 0 to 7) in the absence of predictors. Whether this low risk is negligible remains to be established. In our opinion, most young patients (≤65 years) with a normal ECG and no history of heart failure will not require additional cardiac investigations to identify arrhythmias as a cause of syncope unless there are other specific reasons to suspect such disease. On the other hand, investigations, and sometimes hospital admission, aiming at diagnosing other nonarrhythmic causes of syncope, should be continued.

Published clinical and epidemiologic studies on syncope already have correlated the presence of arrhythmias as a cause of syncope with age, left ventricular dysfunction, and abnormal ECG.[14-17] The advantage of a prediction score over implicit evaluation by clinicians lays in its explicitness and, therefore, its standardization. Risk-score models, however, only predict an outcome in a group of patients and are formulated to improve, and not replace, the efficiency and accuracy of a physician's judgment. Importantly, the score was developed and validated in hospitals considered as primary and tertiary care institutions, where the prevalence of arrhythmias as a cause of syncope was respectively 17% (derivation cohort) and 18% (validation cohort). This figure may be higher compared with community hospitals or outpatient settings evaluating patients with a presumably lower prevalence of arrhythmias, where our results may not be applicable.

Although it used different outcomes, one emergency-based study previously has attempted to identify factors defining low- and high-risk groups with syncope to assist in the triage decision.[18] Four predictors of arrhythmias or 1-year mortality were identified: a history of ventricular arrhythmias, an abnormal ECG, age >45 years, and a history of congestive heart failure. That predictors of mortality in patients with unexplained syncope are virtually the same as predictors of arrhythmias lends further credibility to our model. Of note, the derivation and validation phases of the study were performed at a single institution, whereas validation in a new population provides the clinician stronger inferences about the usefulness of the rule.[19] Although performed in different patient populations, two additional studies found that the presence of heart disease and an abnormal ECG were also predictors of cardiac arrhythmias.[20,21]

LIMITATIONS

Our study has several limitations. First, one problem in the evaluation of syncope is the lack of a criterion standard against which the results of diagnostic tests can be assessed. Therefore, the definition of diagnostic arrhythmias may depend on which tests are used and how extensively and frequently patients are evaluated. Indeed, even electrophysiologic findings cannot
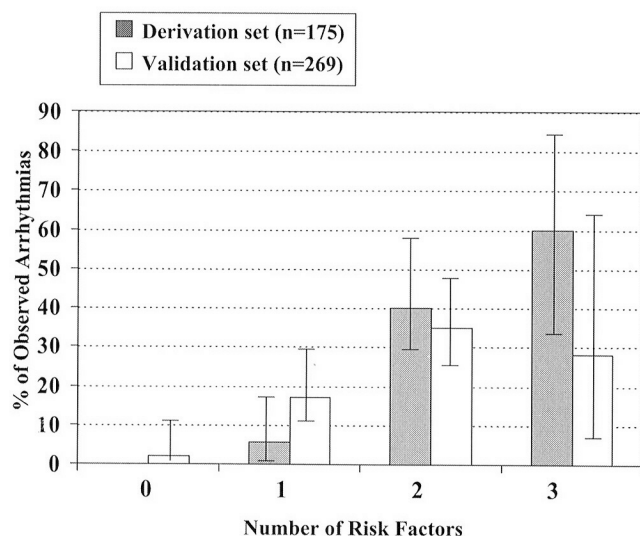
exclude an arrhythmic cause of syncope, although the combined absence of conduction disorder on ECG and structural heart disease strongly predicts a negative outcome. Second, the validation cohort predates the derivation cohort by about 10 years, which questions the comparison between the two diagnostic approaches. Our model, however, was developed only to predict serious and life-threatening arrhythmias as a cause of syncope, and in both cohorts we used similar diagnostic work-up, as well as restrictive and explicit arrhythmia endpoints that are in agreement with recent guidelines.[7] Obviously, the systematic use of recent diagnostic tests such as tilt-table testing would decrease the proportion of patients remaining with syncope of unknown origin; however, it would not change our results with respect to arrhythmia prediction. Finally, the predictive model we developed performed noticeably less well in the validation set than in the development set, although the predictive performance was still substantial. The main difference between the two cohorts was patients' age. Patients in the derivation set were older, and the association between age and arrhythmias was stronger than in the validation set. Because of this discrepancy, the value of age older than 65 years as a predictor of arrhythmias remains uncertain.

CONCLUSIONS

In patients with unexplained syncope after ED assessment, a risk score based on clinical and ECG features may help to predict the risk of arrhythmias as the cause of syncope. Future studies can use risk stratification to facilitate decision making regarding the need for in-hospital admission and/or extensive cardiovascular evaluation in higher-risk subsets.

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